IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Berzofsky et al.

Application No. 10/532,374

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For: METHODS TO PREVENT TUMOR RECURRENCE BY BLOCKADE OF TGF-BETA

Examiner: Sheela J. Huff

Art Unit: 1643

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants request review of the final rejection in the above-identified application. No amendments are being filed with this request. The Final Office action dated August 21, 2009 indicates that claims 46-72 remain rejected under 35 U.S.C. §103(a). This request is being filed with a Notice of Appeal. Review is requested for at least the reasons stated below.

The Claimed Invention

The subject claims (copy attached as **Exhibit A**) are directed to a method of inhibiting tumor recurrence in a subject using a monoclonal antibody obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849), or a humanized equivalent thereof, wherein the antibody is specific for TGF-β and neutralizes an activity of TGF-β.

35 U.S.C. §103 Rejections

The Cited References

Claims 46-50, 52-55, 59-67, 69, and 71 are rejected under 35 U.S.C. §103 as allegedly unpatentably obvious over Dasch *et al.* (U.S. Patent No. 6,090,383) in view of PCT Application No. WO 00/01410, Barbera-Guillem (U.S. Patent No. 6,224,866), Rosenblum (U.S. Patent Application No. 2005/0214307), and Zavada *et al.* (U.S. Patent No. 6,297,041). Claims 46-55 and 59-72 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.*, and Suthanthiran *et al.* (U.S. Publication No. US 2004-0197333). Claims 46-72 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.*, WO 00/01410, Barbera-

Guillem, Rosenblum, Zavada *et al.*, and Terabe *et al.* (*Nature Immunology*, 1:515-520, 2000). Applicants strenuously traverse these rejections. All of these references are already available in the record.[1]

Inhibiting Versus Treating Tumor Recurrence

The pending claims are directed to methods of *inhibiting* a tumor recurrence and **not** to *treating* a tumor recurrence. As discussed in the Declaration under 37 C.F.R. 1.132, from Inventor Jay A. Berzofsky, M.D., Ph.D. (Declaration – **Exhibit B**; originally submitted with the Response to Non-Final Action on June 11, 2009), "the actions of "inhibiting" and "treating" are very different, as methods of inhibiting a tumor recurrence are prophylactic and are used to prevent a tumor from *developing*, whereas methods of treating a tumor recurrence are directed against an *existing* tumor" (Declaration at paragraph 3). Moreover, it is recognized in the art that "the effectiveness of an agent for *treating* a tumor recurrence does not predict the effectiveness of the same agent for *inhibiting* the recurrence" (Declaration at paragraph 3; see also Declaration at paragraphs 5 and 6). Thus, Applicants strenuously submit that the phrase "treating a recurrence" cannot be equated with "inhibiting a recurrence" and a reference that only discloses that an agent can be used to *treat* a tumor recurrence does not teach (explicitly or inherently, or by predictable inference) *inhibiting* tumor recurrence.[2]

The Rejections Vis-à-Vis the Cited References

The emphasis in the current USPTO Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.* is the **predictability** of the combination, as a basis for a finding that there is a reasonable expectation of success of obtaining the Applicants' invention associated with a prior art combination. It is respectfully submitted that in the present case, there is no such element of predictability in the purported combination of references, and accordingly no reasonable expectation of success and, therefore, no obviousness.

Claims 46-50, 52-55, 59-67, 69, and 71 are rejected under 35 U.S.C. §103 as obvious over Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* because the combination of references allegedly teaches that "compounds that *treat* tumors can also be used to *treat* tumor recurrence" (February 11, 2009 Office action at page 4; emphasis added). As admitted in the Office action, Dasch *et al.* does not discuss the treatment of tumor recurrence (nor does Dasch *et al.* disclose methods of *inhibiting* tumor recurrence). WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* each disclose antibodies, **but that is where the similarity with Applicants' claimed methods ends**. WO 00/01410 discloses that anti-TGF-β antibodies can be used "to *detect or quantify* the TGF-β . . . to *diagnose or predict* the occurrence or recurrence of a cancer" (WO 00/01410, page 24, lines 7-9;

[1] For a detailed discussion of the cited references and arguments relating to rejections based on these references, see the Response to Non-Final action dated June 11, 2009.

[2] For a detailed discussion of the distinction between the terms "treatment" and "inhibition," see the discussion at pages 9-10 of the Response to Non-Final Office action dated June 11, 2009.

emphasis added). Thus, this reference teaches that an anti-TGF-β antibody can be used to quantify the amount of TGF-β as *a measure of potential recurrence*. However, there is no teaching in WO 00/01410 that a detectable level of TGF-β is a specific marker of recurrence or that anti-TGF-β antibodies can be used to *inhibit* recurrence, specifically. It is well known in the art that "antibodies are unpredictable" (Declaration at paragraph 7). Thus, Applicants strenuously submit that "one of skill in the art *would not be able to predict* that an antibody used for *detection* also would be effective at *inhibition* of tumor recurrence, without first having demonstrated that the antibody can function to both detect and inhibit tumor recurrence" (Declaration at paragraph 7; emphasis added), nor would one of skill in the art equate "detection" with "inhibition" (see Declaration at paragraph 7). Accordingly, WO 00/01410 is not relevant to the claimed method, **nor is it predictive** in any way (alone or in combination with the other cited references) of Applicants' use of this antibody to inhibit tumor recurrence.

Barbera-Guillem discloses the use of an immunotherapeutic composition that binds directly to B cells in order to cause *B cell depletion* and thereby reduce a pro-tumor immune response. Barbera-Guillem does not teach the 1D11.16 antibody, nor does it teach any other antibody that can bind soluble TGF-β. In contrast, the 1D11.16 antibody of the claimed methods binds TGF-β and blocks an immunosuppressive effect of TGF-β in order to increase immunosurveillance by B cells or T cells (see the specification at page 19, lines 23-32 and Example 5). In other words, the 1D11.16 antibody acts to *increase the biological activity* of B cells and T cells, whereas the antibody disclosed in Barbera-Guillem effectively *decreases the biological activity* of B cells by depleting them. Thus, Barbera-Guillem teaches away from using an antibody to increase the biological activity of B cells and T cells, and the antibodies disclosed in Barbera-Guillem provide no reliable guidance for the activities exhibited by the 1D11.16 antibody. Accordingly, Barbera-Guillem is not relevant to the claimed method, **nor is it predictive** in any way (alone or in combination with the other cited references) of Applicants' use of the 1D11.16 antibody.

Rosenblum discloses that one specific agent used in the treatment of tumors can be used to prevent tumor recurrence (paragraph [0043]). The "agent" of Rosenblum is an immunoconjugate comprised of a monoclonal antibody or a single chain antibody linked to a cytotoxic moiety. However, the "antibody" disclosed in Rosenblum is not, *per se*, inhibiting the tumor recurrence; it is simply targeting the anti-tumor cytotoxin to the tumor cell. Rosenblum does not disclose the 1D11.16 antibody or another antibody that inhibits TGF-β activity. The mere fact that Rosenblum (or any reference) discloses an antibody that targets a tumor protein is not, on its own, predictive of Applicants' claimed methods, which use a completely different antibody in an unpredicted application. Nothing about the Rosenblum agent would provide reliable guidance to one of ordinary skill in the art for the activities exhibited by the 1D11.16 antibody. Accordingly, Rosenblum is not relevant to the claimed method, **nor**

is it predictive in any way (alone or in combination with the other cited references) of Applicants' use of this antibody.

Zavada *et al.* discloses the use of (i) antibodies directed against an oncoprotein (the MN protein) to *treat* cancer patients expressing the MN protein (column 10, lines 42-44) and (ii) anti-idiotype antibodies to MN-specific antibodies (mimics of the MN protein), in a vaccine to *inhibit recurrence* of a MN-expressing tumor (column 11, lines 5-9). However, the assertion by the Office that "Zavada *et al.* discloses [that] the same compounds (which include polypeptides and antibodies) can be used for treatment and [inhibition] of recurrence" (Office action at page 5) is neither accurate nor relevant to Applicants' invention, as claimed, because Applicants' claims are directed to one specific antibody having a specific function, not to an entire class of compounds (antibodies), each having a different function. For example, although an anti-MN antibody and an anti-idiotype antibody are both antibodies, they are different antibodies that bind different antigens and have different functions (treating a tumor or inhibiting a recurrence). As Zavada *et al.* does not teach that one specific agent can be used to both treat a tumor and inhibit a recurrence, one of skill in the art **would not have predicted** the claimed method in view of this reference (alone or in combination with the other cited references).

In order to support a conclusion that a claimed method is obvious, the USPTO must show the **predictability** of the combination of cited references as a basis for a finding that there is a reasonable expectation of success of obtaining the Applicants' invention. Applicants respectfully submit that combining the cited references would not have yielded predictable results to one of skill in the art. Of the cited references, only Dasch *et al.* discloses the 1D11.16 antibody. WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* each disclose antibodies, **but the antibodies are not acting in the same manner that the 1D11.16 antibody is acting in Applicants' invention**. As discussed above, antibodies are inherently unpredictable. Thus, the mere fact that a reference discloses an antibody is not, on its own, predictive of Applicants' claimed methods, which use a completely different antibody in an unpredicted manner. Moreover, with regard to the use of an antibody for treatment or inhibition of tumors specifically, the cited references disclose a completely different type of antibody from that of the claimed methods (not an anti-TGF-β antibody) that functions in a different manner in the cell. Thus, nothing about the combined disclosures of WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* would provide reliable guidance to one of ordinary skill in the art for the activities exhibited by the 1D11.16 antibody (inhibiting tumor recurrence by decreasing TGF-β function). Moreover, nothing in the references, when considered in combination, teaches or predicts that (i) an antibody can *inhibit recurrence* of a tumor by blocking an immunosuppressive effect of TGF-β, or (ii) a specific antibody used to treat a tumor recurrence can also be used to inhibit a tumor recurrence. In view of the above

discussion, Applicants submit that claims 46-50, 52-55, 59-67, 69, and 71 are not *prima facie* obvious and request that this rejection be withdrawn.

Claims 46-55 and 59-72 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.,* and Suthanthiran *et al.* (U.S. Publication No. US 2004-0197333) because Suthanthiran *et al.* discloses the use of TGF-β antagonists, including monoclonal antibodies, "to *treat* a variety of different cancers known to be associated with TGF-β" (Office action at page 7, emphasis added). Claims 46-72 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.,* and Terabe *et al.* (*Nature Immunology*, 1:515-520, 2000) because Terabe *et al.* shows that the "assays of claims 56-58 are known in the art . . . and are used in tumor immunosurveillance" (Office action at page 9). As discussed above in detail, the combined disclosures of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* are **not predictive** of an anti-TGF-β antibody which *inhibits* tumor recurrence. Neither Suthanthiran *et al.* or Terabe *et al.* teaches the use of TGF-β antagonists to inhibit the recurrence of a tumor that has escaped tumor immunosurveillance. Thus, nothing about Suthanthiran *et al.* or Terabe *et al.* would provide reliable guidance to one of ordinary skill in the art for the activities exhibited by the 1D11.16 antibody (inhibiting tumor recurrence). Accordingly, Applicants submit that claims 46-55 and 59-72, and claims 46-72, are not *prima facie* obvious and request that these rejections be withdrawn.

Conclusion

None of the cited references, when considered in combination, teaches or predicts that (i) an antibody can *inhibit recurrence* of a tumor by blocking an immunosuppressive effect of TGF-β, or (ii) a specific antibody used to treat a tumor recurrence can also be used to inhibit a tumor recurrence. In view of the above discussion, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and request that the rejections of claims 46-72 be withdrawn. As these are the only pending rejections, Applicants request allowance of the case.

Respectfully submitted,
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